Osteoarthritis and Cartilage 20 (2012) 727–735

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Baseline mean and heterogeneity of MR cartilage T_2 are associated with morphologic degeneration of cartilage, meniscus, and bone marrow over 3 years – data from the Osteoarthritis Initiative

G.B. Joseph †*, T. Baum †, H. Alizai †‡, J. Carballido-Gamio †, L. Nardo †, W. Virayavanich †, J.A. Lynch §, M.C. Nevitt §, C.E. McCulloch §, S. Majumdar †, T.M. Link †

† *Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA, USA*
‡ *Department of Radiology, University of Texas, San Antonio, Texas USA*
§ *Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA, USA*

ARTICLE INFO

Article history:
Received 2 November 2011
Accepted 4 April 2012

Keywords:
Osteoarthritis
Cartilage
T_2 mapping
Magnetic Resonance Imaging
Osteoarthritis Initiative

SUMMARY

Objective: The purpose of this study is to determine whether the mean and heterogeneity of magnetic resonance (MR) knee cartilage T_2 relaxation time measurements at baseline are associated with morphologic degeneration of cartilage, meniscus, and bone marrow tissues over 3 years in subjects with risk factors for osteoarthritis (OA).

Design: Subjects with risk factors for OA ($n = 289$) with an age range of 45–55 years were selected from the Osteoarthritis Initiative (OAI) database. 3.0 Tesla MR images were analyzed using morphological gradings of cartilage, bone marrow and menisci whole-organ magnetic resonance imaging scores (WORMS scoring). A T_2 mapping sequence was used to assess the mean and heterogeneity of cartilage T_2 (gray level co-occurrence matrix texture analysis). Regression models were used to assess the relationship between baseline T_2 parameters and changes in morphologic knee WORMS scores over 3 years.

Results: The prevalence of knee abnormalities in the cartilage ($P < 0.0005$), meniscus ($P < 0.00001$), and bone marrow significantly ($P < 0.00001$) increased from baseline to 3 years in all compartments combined. The baseline mean and heterogeneity of cartilage T_2 were significantly ($P < 0.05$) associated with morphologic joint degeneration in the cartilage, meniscus and bone marrow over 3 years.

Conclusions: The prevalence of knee abnormalities significantly increased over 3 years; increased cartilage T_2 at baseline predicted longitudinal morphologic degeneration in the cartilage, meniscus, and bone marrow over 3 years in subjects with risk factors for OA.

Published by Elsevier Ltd on behalf of Osteoarthritis Research Society International.

Introduction

Osteoarthritis (OA) is a heterogeneous disease characterized by joint degeneration including the progressive loss of hyaline articular cartilage, development of subchondral sclerosis, and degradation of the meniscus and bone marrow. While OA typically demonstrates gross morphologic changes in the joint, the initial degenerative changes occur on a cellular level, and can be quantified using novel Magnetic Resonance Imaging (MRI) techniques. The early stages of cartilage degeneration include proteoglycan loss, increased water content, and disorganization of the collagen network, which lead to morphologic degeneration. MRI T_2 relaxation time is a technique sensitive to early biochemical changes in cartilage, including water content[1], and collagen fiber orientation[2] and has been proposed as a marker for early OA. Previous studies have demonstrated that mean cartilage T_2 relaxation time is significantly elevated in subjects with OA[3,4], signifying degenerative changes in the collagen structure/content and mobility of water in the extracellular matrix (ECM)[5]. In addition to mean T_2, gray level co-occurrence matrix (GLCM) texture analysis, a method developed by Haralick *et al.*[6], has been used to assess the spatial distribution of cartilage T_2. Preliminary studies have shown that

* Address correspondence and reprint requests to: Gabby B. Joseph, Department of Radiology, UCSF, 1700 4th Street, Suite 203, San Francisco, CA 94158, USA. Tel: 1-415-476-3702; Fax: 1-415-514-9656.

E-mail addresses: gabby.joseph@ucsf.edu (G.B. Joseph), thomas-baum@gmx.de (T. Baum), Alizai@uthscsa.edu (H. Alizai), Julio.Carballido-Gamio@ucsf.edu (J. Carballido-Gamio), Lorenzo.Nardo@ucsf.edu (L. Nardo), Warapat.Virayavanich@ucsf.edu (W. Virayavanich), JLynch@psg.ucsf.edu (J.A. Lynch), MNevitt@psg.ucsf.edu (M.C. Nevitt), CMcCulloch@epi.ucsf.edu (C.E. McCulloch), sharmila.majumdar@ucsf.edu (S. Majumdar), Thomas.Link@ucsf.edu (T.M. Link).

1063-4584/$ – see front matter Published by Elsevier Ltd on behalf of Osteoarthritis Research Society International.
doi:10.1016/j.joca.2012.04.003

subjects with OA have a more heterogeneous distribution of T_2 values than controls[7–9], demonstrating that the mean and heterogeneity of cartilage T_2 pixels may be indicative of early cartilage matrix degeneration. The current study aims to further evaluate the potential of cartilage T_2 as a marker for morphologic degenerative knee changes in OA, by studying the longitudinal evolution of OA in subjects with risk factors for the disease.

The Osteoarthritis Initiative (OAI; http://www.oai.ucsf.edu/) is a multi-center, longitudinal study aimed at assessing biomarkers in OA including those derived from MR imaging. The OAI is a cross-sectional and longitudinal dataset that includes both MRI and radiographic images of subjects scanned annually over 8 years, of which 3 years are currently available. This database provides a means to longitudinally evaluate MRI biomarkers including T_2 relaxation time in the development and progression of OA, thus providing a wealth of information on OA development and progression.

The purpose of this study is to determine whether the mean and heterogeneity of MR knee cartilage T_2 relaxation time measurements at baseline are associated with morphologic degeneration of cartilage, meniscus, and bone marrow tissues over 3 years in subjects with risk factors for OA.

Methods

Subjects

A subset of subjects ($n = 289$) from the incidence cohort of the OAI was selected for this study, as described below. Subjects in the incidence subcohort did not have symptomatic knee OA, defined as frequent symptoms and radiographic OA in the same knee, in either knee at baseline. Frequent knee symptoms were defined as 'pain, aching, or stiffness in or around the knee on most days for at least 1 month during the past 12-months'. Radiographic knee OA was defined as definite tibiofemoral osteophytes (OARSI atlas grades 1–3, equivalent to Kellgren and Lawrence (KL) grade ≥ 2 on fixed flexion radiographs) in either knee at baseline[10]. However, participants in this cohort had risk factors for OA including knee symptoms without radiographic OA, overweight (ages 45–69 males $>$ 205 lbs, females $>$ 170 lbs), (knee injury, knee surgery, family history of total knee replacement, or Heberden's Nodes[10]). The exclusion criteria for the OAI included rheumatoid arthritis, bilateral total knee joint replacement, and a positive pregnancy test. For this study, we specifically included subjects with an age range of 45–55 years. Such individuals are of interest, as they may most benefit from treatment or behavioral interventions. Based on these criteria, 1055 subjects were eligible for the study. Of those, every third subject ($n = 352$) was randomly selected to account for timing of cartilage segmentation and whole-organ magnetic resonance imaging scores (WORMS) readings. Next, subjects with KL grades > 2 and subjects with missing follow-up images were excluded, yielding a final sample size of $n = 289$. The following OAI datasets were assessed in this study: baseline clinical dataset 0.2.2, baseline imaging datasets 0.E.1 and 0.C.2, 36 month follow-up clinical dataset 5.2.1, and 36 month follow-up imaging datasets 5.E.1 and 5.C.1. All OAI study participants signed consent forms for participation in the study.

Knee radiographs

Bilateral standing posterior–anterior fixed flexion knee radiographs were acquired at baseline. Knees were positioned in a Plexiglas frame (SynaFlexer, CCBR-Synarc, Newark, CA, USA) with 20°–30° flexion and 10° internal rotation of the feet. Right knee radiographs were graded by two radiologists (LN with 4-years of experience and WV with 7-years of experience) in consensus by using the KL scoring system[11].

MR imaging

MR images were obtained using four identical 3.0 Tesla (Siemens Magnetom Trio, Erlangen, Germany) scanner and quadrature transmit-receive coils (USA Instruments, Aurora, OH, USA) in Columbus, Ohio; Baltimore, Maryland; Pittsburgh, Pennsylvania; Pawtucket, Rhode Island. The following sequences were acquired and used for image analysis: sagittal two dimensional (2D) intermediate-weighted fast spin-echo sequence (TR/TE = 3200/30 ms, spatial resolution = 0.357 mm × 0.511 mm, slice thickness = 3.0 mm), coronal 2D intermediate-weighted fast spin-echo sequence (TR/TE = 3700/29 ms, spatial resolution= 0.365 mm × 0.456 mm, slice thickness = 3.0 mm), sagittal three dimensional (3D) dual-echo in steady state sequence (TR/TE = 16.3/4.7 ms, spatial resolution = 0.365 mm × 0.456 mm, slice thickness = 0.7 mm) and a 3D fast low angle shot sequence with selective water excitation (TR/TE = 20/7.57 ms, spatial resolution = 0.313 mm × 0.313 mm, slice thickness = 1.5 mm). A sagittal 2D multi-slice multi-echo sequence (MSME, TR = 2700 ms, TE_1–TE_7 = 10–70 ms, spatial resolution = 0.313 mm × 0.446 mm, slice thickness = 3.0 mm, and 0.5 mm gap) was used for T_2 measurements[12].

WORMS scoring

MR images of the right knee obtained at baseline and after 3-years were reviewed on picture archiving communication system (PACS) workstations (Agfa, Ridgefield Park, NJ, USA). MR images were read with baseline and follow-up paired and in known chronological order. A board certified radiologist (WV) with 7-years of experience and a 5th-year radiology resident (LN) with 4-years of experience read the images independently and graded meniscal and cartilage lesions as well as bone marrow edema pattern (BMEP). Cartilage lesions and BMEP were assessed in five compartments (patella, medial femur, medial tibia, lateral femur and lateral tibia) using a modified semi-quantitative WORMS[13–15], with the highest grade of lesion recorded for each region. In case of disagreement, a consensus reading was performed with a musculoskeletal radiologist with 22-years of experience (TML). For calibration purposes, the first 20 cases were read simultaneously by the three readers in consensus. Compared to the original WORMS grading system, only five compartments were analyzed as relatively mild lesions were expected. This could have potentially affected the number of grade 4 or grade 6 cartilage lesions as well as grade 3 BME lesions, all of which, however, are rare. The trochlea was not analyzed because T_2 measurements were not quantified in this compartment due to flow artifacts from the popliteal artery (that may have affected the accuracy of quantification). Cartilage signal and morphology were scored using an eight-point scale: 0 = normal thickness and signal; 1 = normal thickness but increased signal on T_2-weighted images; 2.0 = partial-thickness focal defect $<$1 cm in greatest width; 2.5 = full-thickness focal defect $<$1 cm in greatest width; 3 = multiple areas of partial-thickness (grade 2.0) defects intermixed with areas of normal thickness, or a Grade 2.0 defect wider than 1 cm but $<$75% of the region; 4 = diffuse ($\geq$75% of the region) partial-thickness loss; 5 = multiple areas of full-thickness loss (grade 2.5) or a grade 2.5 lesion wider than 1 cm but $<$75% of the region; 6 = diffuse ($\geq$75% of the region) full-thickness loss. Meniscal morphology was assessed in six regions using a modified WORMS score: the medial and lateral sides of the anterior, body, and posterior region; an additional grade was added to the meniscal classification "intrasubstance degeneration" to better assess early degenerative disease. The grading scale ranged from 1 to 4: 0 = normal, 1 = intrasubstance abnormalities, 2 = non-displaced tear,

3 = displaced or complex tear, and 4 = complete destruction. Subarticular bone marrow abnormalities were defined as poorly marginated areas of increased signal intensity in the normal subchondral and epiphyseal bone marrow on T_2-weighted fast spin-echo fast-suppressed MR images. A four-point grading scale was employed to assess the size of the bone marrow abnormalities: 0 = none, 1 = minimal (<25% of region); 2 = moderate (25–50% of region); and 3 = severe (>50% of region)[16].

Image analysis

All images were analyzed using a Sun Workstation (Sun Microsystems, Palo Alto, CA, USA). Knee articular cartilage was segmented manually in five compartments: (patella, medial femur, medial tibia, lateral femur and lateral tibia) as previously reported[16,17]. An IDL software routine was implemented to manually segment the cartilage from the T_2 maps by one operator (HA). In order to exclude potential chemical shift artifacts or fluid from the region of interest, the user simultaneously examined the T_2 map and the first echo of the MSME sequence (in neighboring image panels) with synchronized cursor/slice number/zoom.

T_2 maps were computed based on equation 1 from the MSME images on a pixel-by-pixel basis using six echoes (TE = 20–70 ms) and three parameter fittings accounting for noise[18,19].

$$S(TE)^2 = S_0^2 e^{-\frac{2*TE}{T_2}} + B^2 \quad (1)$$

In equation 1, S is the signal intensity at a given echo time (TE), S_0 is the signal intensity at $TE = 0$ ms, and B is the estimated noise at a given TE. The first echo (TE = 10 ms) was not included in the T_2 fitting procedure in order to reduce potential errors resulting from stimulated echoes in a multi-echo Carr–Purcell–Meiboom–Gill sequence[20,21]. A noise-corrected algorithm was implemented based on results from a recent study demonstrating increased accuracy and precision of T_2 relaxation time when using with a noise correction algorithm as compared to the traditional uncorrected exponential fit[18,19].

Texture analysis

Texture analysis was performed on a slice-by-slice basis on the cartilage T_2 maps. This method is based on the GLCM as described by Haralick *et al.*[6]. The GLCM determines the frequency that neighboring gray-level values occur in an image. GLCM texture parameters including contrast, variance, and entropy were calculated in each cartilage region. Each texture parameter provides unique information on the spatial distribution of T_2 values in the cartilage. The equations for contrast, variance, and entropy are shown below (equations 2–4), respectively.

$$Entropy = \Sigma_{i=1}^{N} \sum_{j=1}^{N} P(i,j)(-\ln P(i,j)) \quad (2)$$

$$Variance = \sum_{i,j=0}^{N-1} P_{i,j}\left(i - \mu_{i,j}\right)^2 \quad where \quad \mu_{i,j} = \sum_{i,j=0}^{N-1} i(P_{i,j}) \quad (3)$$

$$Contrast = \Sigma_{i=1}^{N} \sum_{j=1}^{N} P(i,j)(i-j)^2 \quad (4)$$

P represents the probability of the co-occurrence of pixel values i and j in an image. N represents the total number of pixel value co-occurrences in the image, and R is a normalizing constant. A pixel offset of 1-pixel was chosen based on the fact that approximately 3–4 pixels span the cartilage thickness. Analysis was performed using averaging the GLCM parameters across four orientations (0°-corresponding to the anterior–posterior axis, 45°, 90°-corresponding to the superior–inferior axis, and 135°).

Statistical analysis

Statistical analysis was performed using STATA 11 software (StataCorp, College Station, TX, USA). Three GLCM texture parameters were analyzed (GLCM contrast, GLCM variance, and GLCM entropy), and were regarded as representative parameters from each of the three texture groups (contrast, statistics, and order, respectively)[22]. These texture parameters were selected based on results from previous studies demonstrating their elevation in subjects with OA[8,9,23].

The prevalence of joint abnormalities was expressed as dichotomous variable. The changes in the prevalence of joint abnormalities from baseline to 3-year follow-up were assessed using McNemar's tests.

In addition to McNemar's tests, the prevalence of subjects with incident knee lesions [no lesions at baseline (WORMS = 0) and development of knee lesions at 3-year follow-up (WORMS > 0)] and with progression of knee lesions (knee lesions at baseline (WORMS > 0) that increase in severity at 3-year follow-up) were calculated.

The associations between baseline T_2 parameters and changes in joint morphology over 3 years were assessed in each compartment using logistic regression models with x-standardized coefficients, such that reported coefficients are per a one standard deviation (SD) change in the predictor. Logistic regression models were used for the prediction of a dichotomous outcome variable. The outcome variable was: subjects with no changes in joint morphology over 3 years (Δ WORMS = 0) vs subjects with increases in joint morphology over 3 years (Δ WORMS > 0). The regression models were adjusted for baseline age, gender, body mass index (BMI), and KL score.

The analyses were subdivided into primary and exploratory compartmental predictors. The primary predictors focused on compartments with the highest prevalence of abnormalities to minimize errors due to multiple comparisons. Thus, the (1) patellar cartilage (2) posterior horn of the medial meniscus and (3) patellar BMEP were assessed. The remaining compartments were examined in an exploratory manner.

Reproducibility measurements

The reproducibility of WORMS scoring for meniscus, cartilage and bone marrow lesion tissues was investigated in 15 subjects, read twice by two radiologists independently. An intra-class correlation coefficient (ICC) was calculated to determine the intra- and inter-reader reproducibility errors[24]. The reproducibility of mean T_2 and texture analysis was determined by segmenting the cartilage in 15 subjects, three times by one operator (HA). The reproducibility error was calculated as the root mean square (RMS) coefficient of variation (CV) of the repeated measurements as described by Glüer *et al.*[25].

Results

Baseline subject characteristics

The mean age of the subject cohort ($n = 289$) was 50.73 ± 2.89 years and the mean BMI was 27.71 ± 4.47 kg/m^2. Other subject characteristics are listed in Table I.

Table I
Subject characteristics

Characteristic	Incidence cohort
n	289
Age (years)	50.73 ± 2.89
BMI (kg/m^2)	27.71 ± 4.47
n (females)	136 (47.0%)
WOMAC pain score	0.98 ± 2.54
n (KL score 0)	182 (62.9%)
n (KL score 1)	89 (30.7%)
n (KL score 2)	18 (6.2%)

Reproducibility

The reproducibility results are listed in Table II. In summary, the intra-observer reproducibility in all tissues (meniscus, cartilage, bone marrow) was ≥96%, while the inter-observer reproducibility was ≥97%. The mean T_2 values had RMS CV ranging from 0.83% in the medial femur to 3.21% in the patella. GLCM entropy exhibited the lowest CVs (<3%), while contrast and variance had CVs <7.2%.

Prevalence and progression of knee abnormalities

Of all tissues, cartilage lesions were the most prevalent: 238 subjects (82.35%) had at least one lesion at baseline and 250 subjects (86.50%) had at least one lesion at follow-up (Table III). Meniscus lesions were second-most in prevalence (191 subjects, 66.09% at baseline; and 212 subjects, 73.36% at follow-up; Table III) followed by BMEP (139 subjects, 48.43% at baseline; and 169 subjects, 58.48% at follow-up; Table III).

The patella demonstrated the highest rate of cartilage abnormalities (191 subjects, 66.08% at baseline; 206 subjects, 71.28% at 3-year follow-up; Table III). The highest prevalence of meniscus lesions was located in the medial posterior compartment (161 subjects, 55.70% at baseline; 177 subjects, 61.24% at 3-year follow-up; Table III). The patella also exhibited the highest rate of BMEP abnormalities (78 subjects, 26.98% at baseline; 102 subjects, 35.29% at 3-year follow-up; Table III).

Table II
Reproducibility measurements for WORMS and T_2 measurements. The reproducibility of WORMS scoring was investigated in 15 subjects, read out twice by two readers independently (ICC[24]). The reproducibility (CV%[25]) of T_2 measurements was determined in five subjects segmented three times each by one operator

Tissue	WORMS reproducibility		T_2 reproducibility				
	Reader	ICC	Compartment	T_2 [%]	GLCM contrast [%]	GLCM entropy [%]	GLCM variance [%]
Meniscus							
	Reader 1	0.96					
	Reader 2	0.96					
	Inter-reader	0.97					
Cartilage							
	Reader 1	0.98					
	Reader 2	0.95					
	Inter-reader	0.98					
			Lateral femur	1.23	3.20	1.16	4.06
			Lateral tibia	1.40	4.87	1.44	4.05
			Medial femur	0.83	2.72	1.59	2.04
			Medial tibia	2.44	3.84	2.59	4.40
			Patella	3.21	7.19	2.62	6.64
			Mean	1.82	4.36	1.88	4.24
BMEP							
	Reader 1	0.97					
	Reader 2	0.97					
	Inter-reader	0.97					

The reproducibility (CV%)[25] of T_2 measurements in five subjects segmented three times each by one operator.

Table III
The prevalence of knee abnormalities at baseline and 3-year follow-up. *P* values are based on McNemar's tests

	Baseline	3-year follow-up	*P* value
	n = 289 total	*n* = 289 total	
Meniscus (WORMS > 0)			
Medial anterior	14 (4.84%)	19 (6.57%)	**0.02**
Medial body	63 (21.79%)	71 (24.56%)	**0.01**
Medial posterior	161 (55.70%)	177 (61.24%)	**0.0001**
Lateral anterior	31 (10.72%)	40 (13.84%)	**0.002**
Lateral body	46 (15.91%)	59 (20.41%)	**0.0003**
Lateral posterior	58 (20.06%)	74 (25.60%)	**0.0001**
All compartments*	191 (66.09%)	212 (73.36%)	**0.00001**
Cartilage (WORMS > 0)			
Patella	191 (66.08%)	206 (71.28%)	**0.0001**
Medial femur	69 (23.87%)	77 (26.64%)	**0.0047**
Medial tibia	27 (9.34%)	28 (9.68%)	0.317
Lateral femur	52 (17.99%)	61 (21.10%)	**0.0027**
Lateral tibia	119 (41.17%)	128 (44.29%)	**0.0027**
All compartments*	238 (82.35%)	250 (86.5%)	**0.0005**
BMEP (WORMS > 0)			
Patella	78 (26.98%)	102 (35.29%)	**0.0002**
Medial femur	19 (6.57%)	29 (10.03%)	**0.0124**
Medial tibia	11 (3.80%)	13 (4.49%)	0.3173
Lateral femur	17 (5.88%)	23 (7.95%)	0.0833
Lateral tibia	27 (9.34%)	34 (11.76%)	0.0707
All compartments*	139 (48.43%)	169 (58.48%)	**0.00001**

Bold values signify that $P < 0.05$.
* All compartments: data points represent number of subjects with at least one lesion.

The increase in prevalence of knee abnormalities over 3 years was statistically significant ($P < 0.05$) for all meniscus compartments and most cartilage compartments (Table III). For BMEP, only the patella and medial femur compartments showed a significant increase in prevalence over 3 years (Table III).

Table IV reports the percentages of both incident lesions and progression of lesions; subjects with incident knee lesions have no lesions at baseline (WORMS = 0) and develop knee lesions at 3-year follow-up (WORMS > 0), subjects with progression of knee abnormalities have knee lesions at baseline (WORMS > 0) that increase in severity at 3-year follow-up. The medial posterior meniscus had the

Table IV
The prevalence of subjects with (1) *incident knee lesions* (no lesions at baseline (WORMS = 0) and development of knee lesions at 3-year follow-up) (WORMS > 0), and (2) *progression of knee lesions* (knee lesions at baseline (WORMS > 0) that increase in severity at 3-year follow-up)

	Number of subjects with incident lesions	Number of subjects with progression of lesions
Meniscus		
Medial anterior	5 (1.73%)	0 (0.00%)
Medial body	9 (3.11%)	10 (3.46%)
Medial posterior	16 (5.53%)	20 (6.92%)
Lateral anterior	9 (3.11%)	4 (1.38%)
Lateral body	13 (4.49%)	6 (2.07%)
Lateral posterior	16 (5.53%)	2 (0.69%)
Total (knee level)	21 (7.26%)*	31 (10.72%)†
Cartilage		
Patella	15 (5.19%)	34 (11.76%)
Medial femur	8 (2.76%)	10 (3.46%)
Medial tibia	1 (0.34%)	2 (0.69%)
Lateral femur	9 (3.11%)	11 (3.80%)
Lateral tibia	9 (3.11%)	10 (3.46%)
Total (knee level)	12 (4.11%)*	40 (13.84%)†
BMEP		
Patella	33 (11.41%)	14 (4.84%)
Medial femur	13 (4.49%)	2 (0.69%)
Medial tibia	3 (1.03%)	2 (0.69%)
Lateral femur	9 (3.11%)	2 (0.69%)
Lateral tibia	11 (3.80%)	7 (2.42%)
Total (knee level)	40 (13.8%)*	25 (8.65%)†

* Defined as baseline WORMS Max = 0 and delta WORMS Max > 0.
† Defined as baseline WORMS Max > 0 and delta WORMS Max > 0.

highest number of incident lesions (16 subjects, 5.53%) and the highest number of progressing lesions (20 subjects, 6.92%). Interestingly, the lateral posterior meniscus also had a high number of incident lesions (16 subjects, 5.53%) but a low number of progressive lesions (two subjects, 0.69%). The patella had the highest number of incident knee cartilage lesions (15 subjects, 5.19%) and progressing knee lesions (34 subjects, 11.76%) followed by the medial femur (incident lesions: eight subjects, 2.76%; progressing lesions: 10 subjects, 3.46%). Incident and progressing BMEP were most prevalent in the patella (incident lesions: 24 subjects, 8.30%; progressing lesions: 14 lesions, 4.84%).

Association between baseline T_2 parameters and changes in knee morphology

Table V summarizes the results for cartilage, meniscus and bone marrow tissues. This table focuses on joint compartments with the highest prevalence of abnormalities (patellar cartilage, posterior horn of the medial meniscus, and patellar BMEP), and thus reports compartments with the highest statistical significance. The results demonstrate that elevated mean and heterogeneity of T_2 values at baseline predict cartilage, meniscus, and bone marrow degeneration after 3 years. Figure 1 shows representative images from a subject with elevated baseline cartilage T2 parameters and both incidence and progression of morphologic joint degeneration in the medial femoral condyle.

Cartilage

Subjects with longitudinal increases in cartilage lesion scores (Δ cartilage WORMS > 0 over 3-years) had greater baseline mean T_2 values than subjects with no longitudinal changes in cartilage lesion scores (Δ cartilage WORMS = 0 over 3-years) in all compartments. The baseline mean T_2 in the patella was 34.55 ± 7.36 ms in subjects with increasing WORMS scores ($n = 49$) and was 32.50 ± 4.00 ms in subjects with no change in WORMS scores ($n = 240$, odds ratio (OR) per SD change = 1.41, $P = 0.025$). Similar trends were evident for GLCM contrast in the patella (OR per SD change = 1.27, $P = 0.079$). The remaining baseline GLCM texture parameters were elevated in subjects with longitudinal progression of cartilage lesions, but these differences were not significant ($P > 0.05$ for all compartments).

Meniscus

Baseline GLCM entropy of cartilage T_2 was elevated in subjects whose meniscus WORMS scores increased over 3 years (Δ meniscus WORMS > 0) compared to subjects whose meniscus scores did not change (Δ meniscus WORMS = 0), as listed in Table V. Subjects with longitudinal increases in their medial posterior meniscus WORMS scores ($n = 36$) had greater cartilage GLCM entropy at baseline than subjects that had no changes in meniscal WORMS scores in the medial femur (7.02 ± 0.21 vs 6.94 ± 0.20, OR = 2.71, $P = 0.057$) and the medial tibia (6.10 ± 0.37 vs 5.91 ± 0.30, OR per SD change = 2.75, $P = 0.003$).

BMEP

Baseline cartilage T_2 parameters including mean T_2, GLCM variance, and GLCM contrast were elevated in subjects with longitudinal increases in BMEP WORMS scores. The patellar compartment, in particular, demonstrated significant differences between groups in the mean T_2 (Δ BMEP WORMS > 0: 35.08 ± 7.00 ms; Δ BMEP WORMS = 0: 32.36 ± 3.93 ms, OR per SD change = 1.65, $P = 0.003$), GLCM contrast (Δ BMEP WORMS > 0: 348.04 ± 208.04; Δ BMEP WORMS = 0: 282.16 ± 139.13, OR per SD change = 1.57, $P = 0.003$), and GLCM variance (Δ BMEP WORMS > 0: 271.43 ± 173.41; Δ BMEP WORMS = 0: 212.20 ± 100.50, OR per SD change = 1.55, $P = 0.001$), Table V.

Discussion

This study evaluated cartilage biochemical composition and knee joint morphology in subjects with risk factors for OA. Our data

Table V
The association between baseline cartilage T_2 parameters and changes in joint morphology over 3 years

Joint tissue compartment*	Baseline cartilage T_2 parameter	Cartilage texture compartment	OR†	95% confidence interval		*P* Value (adjusted)‡	*P* Values (unadjusted)
Cartilage							
Patella	Mean T_2 (ms)	Patella	1.41	1.04	1.91	**0.025**	**0.013**
	Variance	Patella	1.23	0.96	1.58	0.089	0.068
	Entropy	Patella	0.71	0.42	1.22	0.224	0.110
	Contrast	Patella	1.27	0.97	1.67	0.079	0.570
Meniscus							
Medial posterior	Mean T_2	Medial tibia	1.26	0.96	1.65	0.086	0.135
	Variance	Medial tibia	1.08	0.74	1.57	0.640	0.750
	Entropy	Medial tibia	2.75	1.41	5.35	**0.003**	**0.002**
	Contrast	Medial tibia	1.06	0.74	1.53	0.724	0.815
	Mean T_2	Medial femur	1.16	0.71	1.90	0.542	0.733
	Variance	Medial femur	1.08	0.63	1.73	0.854	0.928
	Entropy	Medial femur	2.71	0.97	7.60	0.057	**0.039**
	Contrast	Medial femur	0.84	0.49	1.45	0.556	0.587
BMEP							
Patella	Mean T_2	Patella	1.65	1.19	2.30	**0.003**	**0.002**
	Variance	Patella	1.55	1.18	2.02	**0.001**	**0.004**
	Entropy	Patella	1.23	0.69	2.17	0.475	0.793
	Contrast	Patella	1.57	1.16	2.13	**0.003**	**0.013**

* The analyses were subdivided into primary and exploratory compartmental predictors. The primary predictors (listed in this table) focused on compartments with the highest prevalence of abnormalities to minimize errors due to multiple comparisons. Thus, (1) patellar cartilage (2) posterior horn of the medial meniscus and (3) patellar BMEP were assessed.

† The associations between baseline T_2 parameters and changes in joint morphology over 3 years were assessed using logistic regression models (adjusted for age, gender, BMI, and KL score) with *x*-standardized coefficients, such that reported ORs are per one SD change in the predictor. The outcome variable was dichotomous: subjects with no changes in joint morphology over 3 years (Δ WORMS = 0) vs subjects with increases in joint morphology over 3 years (Δ WORMS > 0). The SDs of cartilage T_2, GLCM contrast, GLCM variance, and GLCM entropy among all subjects were: 5.12 ms, 146.70, 102.42, 0.54, respectively.

‡ *P* value adjusted for age, gender, BMI, and KL score. *P* values < 0.05 are in bold.

show that increased cartilage T_2 at baseline is associated with longitudinal morphologic degeneration in the cartilage, meniscus, and bone marrow over 3 years in subjects with risk factors for OA. The GLCM contrast, entropy, and variance parameters each provide unique information on the spatial heterogeneity of the cartilage, and each was associated with morphologic joint degeneration. This study highlights the complex interactions between the various joint tissues involved in OA, and suggests that cartilage biochemical composition may play an integral role in the development and progression of morphologic disease.

Morphologic joint degeneration in cartilage is often preceded by biochemical alterations in the ECM. A theory of the potential mechanisms that link cartilage biochemical degeneration to future gross degradation in other joint tissues centers on mechanical loading. Initially, degenerative changes in the ECM disrupt the mechanical properties in cartilage tissue, thus reducing its ability to withstand load. The increasing number of large-diameter collagen fibrils in degenerative cartilage[26] cause the closely-knit collagen network to loosen, thus initiating a transformation from a highly structured entity to a random configuration. Changes to the cartilage matrix result in increased tissue stiffness and increased permeability[27], consequently altering the mechanical loading environment in the joint and predisposing surrounding tissues to damage[28]. Bone tissue, for example, can be indirectly affected by changes in the mechanical properties of cartilage: biochemically compromised cartilage may develop micro-cracks that lead to BME, bleeding, and necrosis[29]. Such a relationship was detected in this study, revealing that disrupted cartilage biochemistry at baseline was predictive of the development and progression of BMEP. Thus, the initial degenerative changes in cartilage biochemical composition may disrupt the delicate equilibrium of joint mechanical loading and consequently lead to morphologic degeneration in the surrounding tissues, as seen in this study over 3-years.

In addition to mean cartilage T_2, this study assessed the spatial distribution of cartilage T_2 pixels using GLCM texture analysis. GLCM contrast is a measure of the differences in neighboring pixel values; high contrast signifies that many pixels with different values are neighboring. GLCM entropy is a measure of disorder in

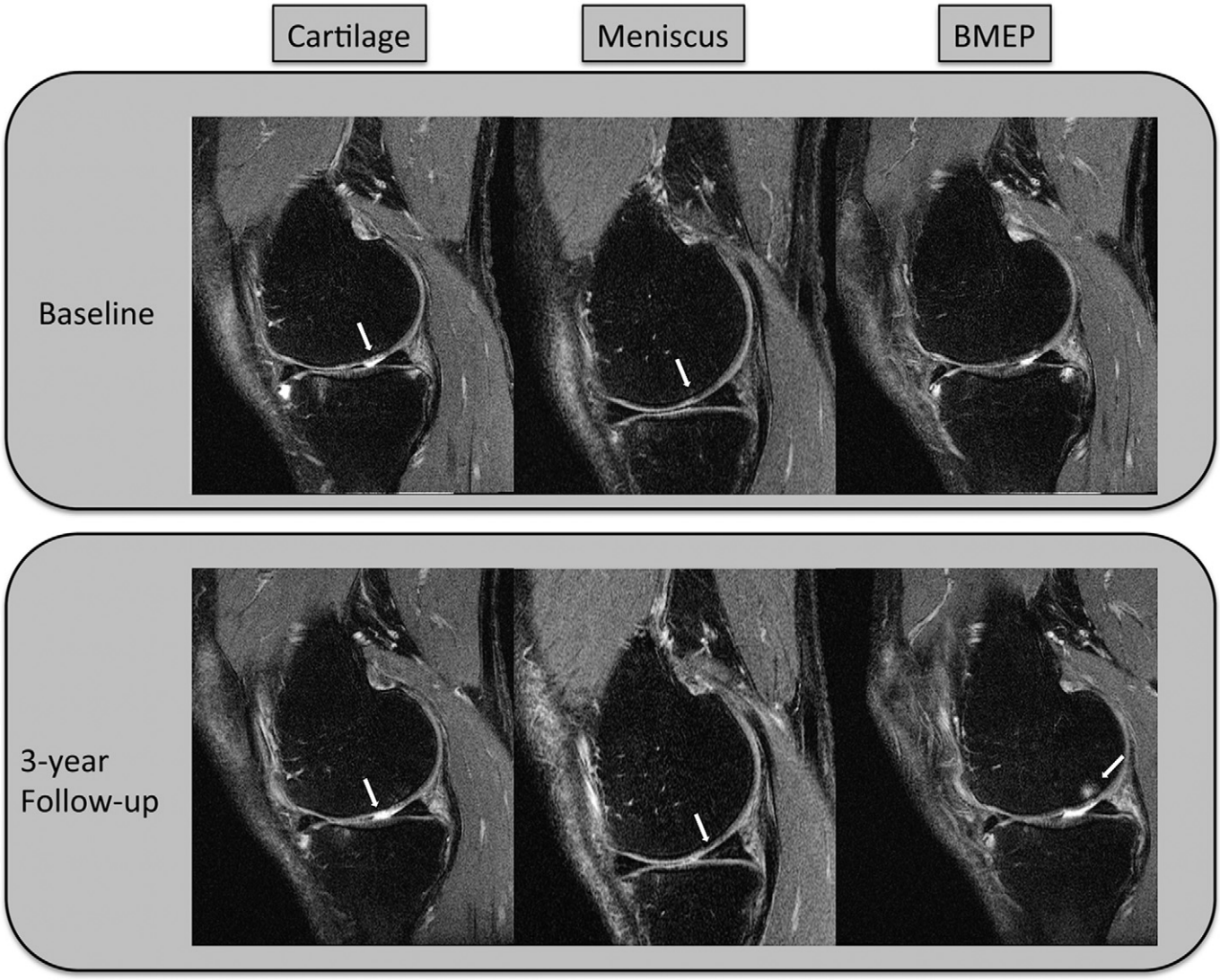

Fig. 1. Representative images (top row: baseline, bottom row: 3-year follow-up) from a subject with elevated baseline cartilage T_2 parameters and both incidence and progression of morphologic joint degeneration in the medial femoral condyle.
Cartilage morphology: progression of cartilage defect (WORMS = 2.5 at baseline, WORMS = 5 at follow-up).
Meniscus morphology: progression from intrasubstance degeneration to a tear (WORMS = 1 at baseline, WORMS = 2 at follow-up).
BMEP morphology: absent at baseline and present at follow-up (WORMS = 0 at baseline, WORMS = 2 at follow-up).

an image; high entropy signifies that the probability of pixel co-occurrence is uniform throughout an image. GLCM variance is a measure of the distribution of pixels about the mean; high variance signifies a high dispersion of co-occurrences of relaxation times. Elevations in the mean and heterogeneity of cartilage T_2 relaxation time are indicative of early cartilage biochemical degeneration, as previously reported[3,8,23,30,31]; Such biochemical changes to the ECM characterize the initial stages of OA, eventually leading to gross joint degeneration, as detected in this study.

Previous research has evaluated the potential of MRI markers in predicting the development of radiographic OA over 6-years[32] and cartilage loss over 2-years[33]. Eckstein *et al.* studied an array of clinical, radiographic, molecular, and MRI-based markers, and reported that cartilage thickness, varus malalignment, reduced joint space width, and joint space narrowing at baseline predicted longitudinal cartilage thinning[33]. In contrast to the results of the current study, T_2 was not predictive of OA progression. While the results of the two studies differ, notable differences are also evident in the methodology and subject selection between the two studies. First, Eckstein *et al.* calculated cartilage T_2 using two echo times, while the current study acquired images with seven echo times; the number of echo times used for quantification may affect the accuracy of T_2 quantification. Second, the subjects in Eckstein *et al.'s* study had KL grades of 2–3 while the majority of subjects in the current study had KL grades 0–1 ($n = 271$); thus a marked difference in disease severity was evident between subject cohorts. Collectively, these studies suggest that the utility of T_2 in predicting morphologic progression may be optimal at early stages of disease, in subjects without pronounced radiographic OA.

In addition to predicting morphologic cartilage degeneration over 3 years, abnormal cartilage biochemical composition at baseline was associated with longitudinal meniscus degradation. The meniscus provides joint stability, lubrication, and shock absorption to the joint[34] and lies adjacent to the articular cartilage; thus degeneration to the meniscus and cartilage tissues is often concomitant[35–37]. Studies have demonstrated a relationship between meniscus morphology and cartilage morphology[35–37] as well as cartilage biochemical composition[38]. Kai *et al.* established an association between meniscus signal-complex tears and increased MRI T_2 values in the tibial articular cartilage[38], and Zarins *et al.* reported an association between the presence of meniscal tears in the posterior horn of the medial meniscus and elevated T_2 values in the medial tibial cartilage[39]. The results of the current study are consistent with those of other studies, highlighting an interaction between cartilage biochemical composition and meniscus degeneration.

The current research is novel, however, in its investigation of the heterogeneity of cartilage pixels in relation to joint morphology. Since the GLCM entropy of cartilage T_2 was related to meniscus degeneration, this study suggests that a heterogeneous distribution of cartilage pixels may be predictive of future degenerative meniscus changes. In contrast to other studies, the mean T_2 was not significantly predictive of meniscus degeneration. These findings may be related to the fact that this study focused on subjects with early or low-grade meniscus degeneration at baseline, while other studies recruited subjects with definite meniscus abnormalities: a majority of the subjects in this study had either no meniscus degeneration (WORMS = 0, $n = 128$) or low-grade intrasubstance abnormalities (WORMS = 1, $n = 93$) at baseline, compared to other studies that evaluated subjects with meniscal tears. As an additional exploratory analysis, the relationship between mean T_2 and morphologic degeneration was assessed in only subjects with meniscal tears at baseline. When confining the analysis to subjects with meniscal tears (WORMS ≥ 2) at baseline, the mean T_2 was predictive of longitudinal meniscus degeneration, which is consistent with other studies[38]. Collectively, these results demonstrate that the spatial distribution and the mean of cartilage T_2 values may be related to different stages of meniscus degeneration, and that these parameters may provide complementary information in the study of OA.

Several limitations are pertinent to this study. Other techniques such as dGEMRIC (delayed gadolinium-enhanced MRI of cartilage) or T1ρ may have been useful in investigating the ECM during OA progression; however, this study did not assess these methods as they were not acquired in the OAI protocol. In addition, a comparison of texture parameters between subjects from the OAI incidence and normal control cohorts would have been of interest; however was not performed due to the time-consuming segmentation process. Finally, the WORMS score has inherent limitations due to its semi-quantitative nature; other quantitative scores such as the UCSF score[40] may be more sensitive in detecting longitudinal changes in joint morphology.

In conclusion, this study demonstrated that the prevalence of knee abnormalities significantly increased over 3 years, and that increased cartilage T_2 at baseline is associated with longitudinal morphologic degeneration in the cartilage, meniscus, and bone marrow over 3 years in subjects with risk factors for OA.

Authors' contributions

GBJ assisted with the study design, performed T_2 assessment, performed statistical analysis, and drafted the manuscript. TB assisted in designing the study, supervised the cartilage segmentation, helped interpret the data, and helped perform the analysis. JCG developed the software for T_2 mapping quantification and texture analysis. LN performed WORMS grading and cartilage segmentations. WV performed WORMS grading. HA performed cartilage segmentation. JAL participated in the study design and patient selection. MCN assisted with data interpretation and manuscript revision. CM advised with and helped perform the statistical analysis. SM participated in the conceptual design of the study, data interpretation, and analysis. TML participated in the design of the study, interpretation of data, performing WORMS scoring, and manuscript revision. All authors have read and approved the manuscript.

Role of the funding source

This study was funded by NIH U01 AR059507 and NIH F32 AR059478.

Competing interests

The authors declare that they have no competing interests.

Acknowledgments

This study was funded by NIH U01 AR055079 and NIH F32 AR059478.

The OAI is a public-private partnership comprised of five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the National Institutes of Health, a branch of the Department of Health and Human Services, and conducted by the OAI Study Investigators. Private funding partners include Pfizer, Inc.; Novartis Pharmaceuticals Corporation; Merck Research Laboratories; and GlaxoSmithKline. Private sector funding for the OAI is managed by the Foundation for the National Institutes of Health.

This manuscript has received the approval of the OAI Publications Committee based on a review of its scientific content and data interpretation.

References

1. Liess C, Lusse S, Karger N, Heller M, Gluer CC. Detection of changes in cartilage water content using MRI T2-mapping in vivo. Osteoarthritis Cartilage 2002;10:907–13.
2. Xia Y. Magic-angle effect in magnetic resonance imaging of articular cartilage: a review. Invest Radiol 2000;35:602–21.
3. Dunn TC, Lu Y, Jin H, Ries MD, Majumdar S. T2 relaxation time of cartilage at MR imaging: comparison with severity of knee osteoarthritis. Radiology 2004;232:592–8.
4. Blumenkrantz G, Lindsey CT, Dunn TC, Jin H, Ries MD, Link TM, *et al*. A pilot, two-year longitudinal study of the interrelationship between trabecular bone and articular cartilage in the osteoarthritic knee. Osteoarthritis Cartilage 2004;12:997–1005.
5. Konig H, Sauter R, Delmling M, Vogt M. Cartilage disorders: a comparison of spin-echo, CHESS, and FLASH sequence MR images. Radiology 1987;164:753–8.
6. Haralick RM, Shanmugam K, Dinstein I. Textural features for image classification. IEEE Trans Syst Man Cybern 1973;SMC-3:610–8.
7. Blumenkrantz G, Dunn TC, Carballido-Gamio J, Link TM, Majumdar S. Spatial Heterogeneity of Cartilage T2 in Osteoarthritic Patients. Boston, MA: OARSI; 2005.
8. Carballido-Gamio J, Stahl R, Gabrielle B, Adan R, Sharmila M. Spatial analysis of magnetic resonance T1rho and T2 relaxation times improves classification between subjects with and without osteoarthritis. Med Phys 2009;36:4059–67.
9. Li X, Pai A, Blumenkrantz G, Carballido-Gamio J, Link T, Ma B, *et al*. Spatial distribution and relationship of T1rho and T2 relaxation times in knee cartilage with osteoarthritis. Magn Reson Med 2009;61:1310–8.
10. Nevitt MC, Felson DT, Lester G. The Osteoarthritis Initiative.
11. Kellgren J, Lawrence J. Radiologic assessment of osteoarthritis. Ann Rheum Dis 1957;16:494–502.
12. Peterfy C, Schneider E, Nevitt M. The osteoarthritis initiative: report on the design rationale for the magnetic resonance imaging protocol for the knee. Osteoarthritis Cartilage 2008;16:1433.
13. Peterfy CG, Gold G, Eckstein F, Cicuttini F, Dardzinski B, Stevens R. MRI protocols for whole-organ assessment of the knee in osteoarthritis. Osteoarthritis Cartilage 2006;14(Suppl A):A95–111.
14. Stahl R, Luke A, Ma CB, Krug R, Steinbach L, Majumdar S, *et al*. Prevalence of pathologic findings in asymptomatic knees of marathon runners before and after a competition in comparison with physically active subjects – a 3.0 T magnetic resonance imaging study. Skeletal Radiol 2008;37:627–38.
15. Peterfy CG, Guermazi A, Zaim S, Tirman PF, Miaux Y, White D, *et al*. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage 2004;12:177–90.
16. Stehling C, Liebl H, Krug R, Lane NE, Nevitt MC, Lynch J, *et al*. Patellar cartilage: T2 values and morphologic abnormalities at 3.0-T MR imaging in relation to physical activity in asymptomatic subjects from the osteoarthritis initiative. Radiology 2010;254:509–20.
17. Stehling C, Baum T, Mueller-Hoecker C, Liebl H, Carballido-Gamio J, Joseph G, *et al*. A novel fast knee cartilage segmentation technique for T2 measurements at MR imaging-data from the osteoarthritis initiative. Osteoarthritis Cartilage 2011;19:984–9.
18. Miller AJ, Joseph PM. The use of power images to perform quantitative analysis on low SNR MR images. Magn Reson Imaging 1993;11:1051–6.
19. Raya J, Dietrich O, Horng A, Weber J, Reiser M, Glaser C. T2 measurement in articular cartilage: impact of the fitting method on accuracy and precision at low SNR. Magn Reson Med 2010;63:181–93.
20. Smith HE, Mosher TJ, Dardzinski BJ, Collins BG, Collins CM, Yang QX, *et al*. Spatial variation in cartilage T2 of the knee. J Magn Reson Imaging 2001;14:50–5.
21. Maier CF, Tan SG, Hariharan H, Potter HG. T2 quantitation of articular cartilage at 1.5 T. J Mag Reson Imaging 2003;17:358–64.
22. Hall-Beyer M. The GLCM Tutorial, http://www.fp.ucalgary.ca/mhallbey/;.
23. Blumenkrantz G, Stahl R, Carballido-Gamio J, Zhao S, Lu Y, Munoz T, *et al*. The feasibility of characterizing the spatial distribution of cartilage T(2) using texture analysis. Osteoarthritis Cartilage 2008;16:584–90.
24. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull 1979;86:420–8.
25. Glüer CC, Blake G, Blunt BA, Jergas M, Genant HK. Accurate assessment of precision errors: how to measure the reproducibility of bone densitometry techniques. Osteoporosis Int 1995;5:262–70.
26. Lipowitz AJ, Newton CD. Degenerative Joint Disease and Traumatic Arthritis. Textbook of Small Animal Orthopaedics. Ithaca: International Veterinary Information Service; 1985.
27. Buckwalter J, Mankin H. Articular cartilage. Part II: degeneration and osteoarthrosis, repair, regeneration, and transplantation. J Bone Joint Surg Am 1997;79:612–32.
28. Garstang SV, Stitik TP. Osteoarthritis: epidemiology, risk factors, and pathophysiology. Am J Phys Med Rehabil 2006;85:S12–4. S2-11; quiz.
29. Imhof H, Sulzbacher I, Grampp S, Czerny C, Youssefzadeh S, Kainberger F. Subchondral bone and cartilage disease: a rediscovered functional unit. Invest Radiol 2000;35:581.
30. Nissi MJ, Toyras J, Laasanen MS, Rieppo J, Saarakkala S, Lappalainen R, *et al*. Proteoglycan and collagen sensitive MRI evaluation of normal and degenerated articular cartilage. J Orthop Res 2004;22:557–64.
31. Mosher TJ, Dardzinski BJ, Smith MB. Human articular cartilage: influence of aging and early symptomatic degeneration on the spatial variation of T2-preliminary findings at 3 T. Radiology 2000;214:259–66.
32. Owman H, Tiderius CJ, Neuman P, Nyquist F, Dahlberg LE. Association between findings on delayed gadolinium enhanced magnetic resonance imaging of cartilage and future knee osteoarthritis. Arthritis Rheum 2008;58:1727–30.
33. Eckstein F, Le Graverand M, Charles H, Hunter D, Kraus V, Sunyer T, *et al*. Clinical, radiographic, molecular and MRI-based predictors of cartilage loss in knee osteoarthritis. Ann Rheum Dis 2011;70:1223.
34. Radin EL, de Lamotte F, Maquet P. Role of the menisci in the distribution of stress in the knee. Clin Orthop Relat Res 1984;185:290.
35. Thomsen J, Straarup T, Danielsen C, Oxlund H, Brüel A. Relationship between articular cartilage damage and subchondral bone properties and meniscal ossification in the Dunkin Hartley guinea pig model of osteoarthritis. Scand J Rheumatol 2011;40:391–9.
36. Hunter DJ, Zhang YQ, Niu JB, Tu X, Amin S, Clancy M, *et al*. The association of meniscal pathologic changes with cartilage loss in symptomatic knee osteoarthritis. Arthritis Rheum 2006;54:795–801.
37. Crema MD, Guermazi A, Li L, Nogueira-Barbosa MH, Marra MD, Roemer FW, *et al*. The association of prevalent medial meniscal

pathology with cartilage loss in the medial tibiofemoral compartment over a 2-year period. Osteoarthritis Cartilage 2009;18:336–43.
38. Kai B, Mann SA, King C, Forster BB. Integrity of articular cartilage on T2 mapping associated with meniscal signal change. Eur J Radiol 2010.
39. Zarins ZA, Bolbos RI, Pialat JB, Link TM, Li X, Souza RB, *et al*. Cartilage and meniscus assessment using T1rho and T2 measurements in healthy subjects and patients with osteoarthritis. Osteoarthritis Cartilage 2010;18:1408–16.
40. Stahl R, Jain SK, Lutz J, Wyman BT, Le Graverand-Gastineau MPH, Vignon E, *et al*. Osteoarthritis of the knee at 3.0 T: comparison of a quantitative and a semi-quantitative score for the assessment of the extent of cartilage lesion and bone marrow edema pattern in a 24-month longitudinal study. Skeletal Radiol 2011;40:1315–27.